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Detection of Microwave Heating in 5-Hydroxytryptamine-Induced Hypothermic Mice

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16. ABSTRACT

The intraperitoneal injection of 5-hydroxytryptamine (5-HT) in unrestrained and unanesthetized mice held at 22°C causes a hypothermia which is maximal after approximately 15 minutes. When mice injected with 5-HT were held in a controlled environment of 22°C and 50% relative humidity and exposed to microwaves (2450 MHz, cw) at 1 mW/cm^2 for 15 minutes, significant increases were observed in the body temperature of these mice compared to 5-HT-treated sham-irradiated mice. The magnitude of the response was related to power density (10 > 5 > 1 mW/cm^2). Saline-injected mice exposed for 15 minutes at 10 mW/cm^2 (specific absorption rate = 7.2 mW/g) showed no significant increase in body temperature compared to saline-injected sham-irradiated mice. The hypothermia induced by 5-HT in mice was also found to be affected by ambient temperature alone. Increases in ambient temperature above 22°C, in the absense of microwaves, caused a concomitant increase in body temperature. By altering the thermoregulatory capacity of mice with 5-HT, subtle heating by microwaves was detected. These results indicate that the interpretation of microwave-induced biological effects observed in animals at comparable power and absorption levels should include a consideration of the thermogenic potential of microwave radiation.

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Detection of Microwave Heating in 5-Hydroxytryptamine-Induced Hypothermic Mice

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SMIALOWICZ, R. J., RIDDLE, M. M., BRUGNOLOTTI, P. L., ROGERS, R. R., AND COMPTON, K. L. Detection of Microwave Heating in 5-Hydroxytryptamine-Induced Hypothermic Mice. *Radiat. Res.* **88**, 108–117 (1981).

The intraperitoneal injection of 5-hydroxytryptamine (5-HT) in unrestrained and unanesthetized mice held at 22°C causes a hypothermia which is maximal after approximately 15 min. When mice injected with 5-HT were held in a controlled environment of 22°C and 50% relative humidity and exposed to microwaves (2450 MHz, cw) at 1 mW/cm^2 for 15 min, significant increases were observed in the body temperature of these mice compared to 5-HT-treated sham-irradiated mice. The magnitude of the response was related to power density ($10 > 5 > 1$ mW/cm^2). Saline-injected mice exposed for 15 min at 10 mW/cm^2 (specific absorption rate = 7.2 mW/g) showed no significant increase in body temperature compared to saline-injected sham-irradiated mice. The hypothermia induced by 5-HT in mice was also found to be affected by ambient temperature alone. Increases in ambient temperature above 22°C, in the absence of microwaves, caused a concomitant increase in body temperature. By altering the thermoregulatory capacity of mice with 5-HT, subtle heating by microwaves was detected. These results indicate that the interpretation of microwave-induced biological effects observed in animals at comparable power and absorption levels should include a consideration of the thermogenic potential of microwave radiation.

INTRODUCTION

Over the years, there has been considerable controversy concerning the potential for microwave radiation to cause biological effects in experimental animals in the absence of detectable increases in body or tissue temperature. In many instances, the effects produced by microwaves have been attributed to direct interactions (i.e., athermal or field-specific effects) unrelated to any detectable temperature change in the biological specimen. Traditionally, claims for microwave-induced effects at 'nonthermal' (lack of measurable thermalization) power densities have come from Soviet and Eastern European laboratories (*1*). More recently, several investigators in the United States have reported microwave-induced biological effects in experimental animals at power densities which did not produce an increase in core temperature. For example, Thomas *et al.* (*2*) reported that microwave radiation (2450 MHz) at a power density of 1 mW/cm^2 modifies the behavioral effects produced by the drug chlordiazepoxide in the absence of a body temperature in-

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crease. Stern *et al.* (*3*) reported that rats held in a cold environment turned on a heat lamp less frequently during microwave exposure than during a preceding control period. This behavioral thermoregulation occurred at 5 mW/cm^2 in the absence of an increase in the core temperature. Adair and Adams (*4*) reported that monkeys held in a cool environment can be induced to surface vasodilation, as indicated by a rapid and persistent temperature rise in the tail skin, in the absence of core temperature increases by brief exposure to 2450-MHz microwave radiation at 8 mW/cm^2. The vasodilatory response to microwaves was found to closely resemble the response produced by direct experimental heating of the hypothalamus.

Using behavioral and physiological thermoregulatory techniques, Stern *et al.* (*3*) and Adair and Adams (*4*) demonstrated that animals could detect subtle heating by microwaves during cold stress at a power density below 10 mW/cm^2. More recently, we reported increases in the core temperature of rats made hypothermic by bacterial endotoxin during exposure to microwaves (2450 MHz) at 1 mW/cm^2 (*5*). Putthoff *et al.* (*6*) also showed increases in the core temperature of rats made hypothermic with cortisone and exposed to microwaves. These results indicate that animals made hypothermic by endotoxin or drugs or subjected to cold stress may be sensitive models for the detection of subtle microwave-induced heating.

To further examine the hypothermia model in another species, 5-hydroxytryptamine was used to produce hypothermia in mice (*7*). We present evidence of significant increases in the core temperature of 5-HT-induced hypothermic mice exposed to 2450-MHz microwaves. Saline-injected mice exposed at identical power densities of microwave radiation showed no core temperature increase. These results provide additional evidence that subtle heating by microwaves can be detected in hypothermic mice as well as rats while such increases in core temperature could not be found in animals (saline-injected) with normal thermoregulatory functions. These findings indicate that the interpretation of microwave-induced biological effects in experimental animals should be prudently evaluated for the role played by microwave heating.

MATERIALS AND METHODS

Mice. Female BALB/C mice (Charles River Labs, Wilmington, MA) or male CBA/J mice (Jackson Labs, Bar Harbor, ME) between 8 and 12 weeks of age were used. The weight of the BALB/C mice was 20–25 g while that of the CBA/J mice was 24–28 g. Mice were maintained in a 12:12 light–dark cycle and allowed food and water *ad libitum*. Animals were not used for experiments for at least 1 week following arrival in our vivarium. All mice were used only once and then after several days of observation were killed.

Animal treatments. Mice were injected intraperitoneally with 0.5 mg of 5-hydroxytryptamine creatinine sulfate complex (Sigma Chemical Co., St. Louis, MO) in a volume of 0.2 ml pyrogen-free saline. This corresponds to a dose of approximately 20–25 mg/kg. Control mice were injected with an equal volume of pyrogen-free saline. All test tubes, syringes, and needles were sterile, disposable, and pyrogen free.

Microwave exposure system. The 2450-MHz exposure system is the same as

that described by Elder and Ali (8). The microwave field was generated by a Varian Model PPS-2.5 AS industrial heating unit at a frequency of 2450 MHz in a continuous-wave mode. A total root-mean-square (RMS) ripple of 11% was measured after the installation of a full-wave bridge in the filament circuit. An environmental exposure chamber (61 × 76 × 76 cm) was composed of foamed polystyrene and was positioned beneath a 10-db-gain pyramidal horn antenna in the far field. The environmental chamber was confined in an anechoic chamber that was lined with microwave-absorbing material (Models CBV and VCVB 24, Emerson and Cuming, Inc., Canton, MA). An environmental control system permitted regulation of the temperature and humidity in the exposure chamber and in an identical foamed polystyrene chamber located outside the anechoic chamber which served as a sham-irradiated chamber. The temperature was maintained at 22 ± 0.5°C, relative humidity at 50 ± 10%, and air flow at 4.3 m^3/min (measured in the air duct leading to the chamber with a thermo-anemometer, Alnor Instrument Co. Niles, IL), unless stated otherwise.

Animal exposures. Immediately prior to 5-HT or saline injection, the colonic temperature of mice was taken. Temperatures were measured with a YSI (Yellow Springs Instrument Co., Yellow Springs, OH) Model 520 thermistor probe inserted 2.5 cm beyond the anal sphincter. The thermistor probe was lubricated with K-Y jelly (Johnson and Johnson, Inc. New Brunswick, NJ). Temperatures were read to an accuracy of 0.1°C from a YSI Model 46 telethermometer.

Following injection, mice were confined individually in vented polycarbonate boxes, 6 cm on edge, and placed in one of four positions of a diamond-shaped array. The mice were spaced equally from each other (19 cm) and 9.5 cm from the center of the microwave exposure chamber. The size of the polycarbonate box allowed the mouse freedom of movement during exposure. Age- and strain-matched injected mice were positioned in a similar array in the sham-irradiation chamber. Mice were irradiated for 15 min at power densities of 10, 5, or 1 mW/cm^2, which are equivalent to specific absorption rates as determined by twin-well calorimetry of 7.2, 3.6, and 0.7 mW/g, respectively, for the BALB/C mice (9). Groups of four microwave-irradiated mice were paired with an equal number of sham-irradiated mice. Irradiations were alternated with sham-irradiations so that colonic temperatures could be most expeditiously obtained. All exposures were performed between 1300 and 1600 hr.

Statistical analyses of comparisons of final colonic temperatures (i.e., temperature following 15 min of exposure) and colonic temperature changes (i.e., ΔT = final temperature minus initial temperature) for irradiated and sham-irradiated mice were done using Student's t test.

RESULTS

Figure 1 shows the time-dependent hypothermic response of BALB/C mice (N = 10) to 5-HT at 22°C. The maximum response occurred approximately 15 min following injection. A similar response was observed for CBA/J mice (data not shown). Consequently, 15 min was chosen as the optimal time for microwave exposures and temperature measurements were made immediately afterward.

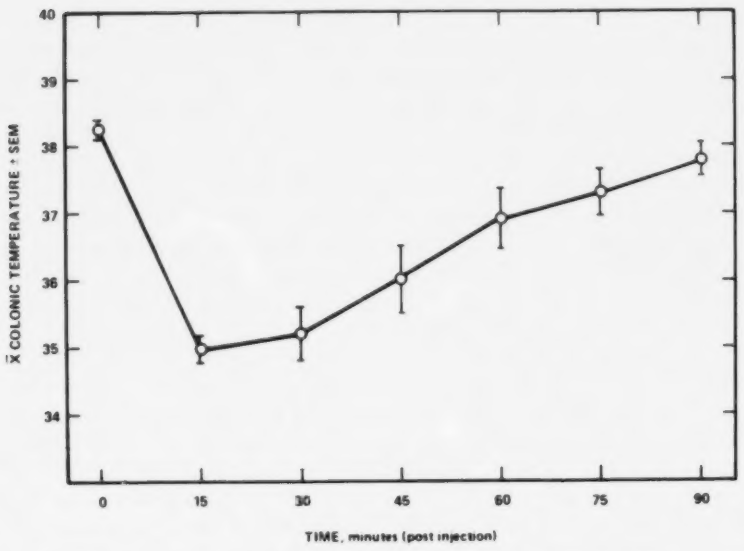

FIG. 1. Time-dependent hypothermic response of BALB/C mice to 5-hydroxytryptamine at 22°C, N = 10. Colonic temperatures were taken every 15 min following injection of 5-HT.

The effect that ambient temperature has on the hypothermic response of 5-HT-treated CBA/J mice is shown in Fig. 2. Six mice were used at each temperature. Core temperature was found to increase with increasing ambient temperature. However, the hypothermic effect of 5-HT was still evident in the mice maintained in this environment.

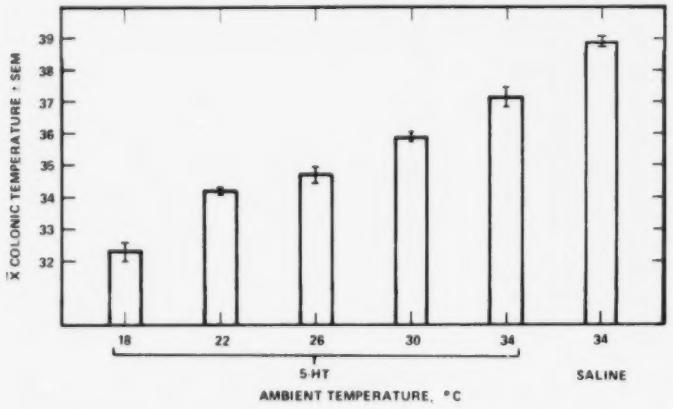

FIG. 2. Effect of ambient temperature on 5-HT-induced hypothermia in CBA/J mice after 15 min. For each temperature, N = 6.

Figure 3 shows the response of 5-HT-treated BALB/C mice to microwaves. At each power density 8–12 mice were used (i.e., 8 mice each for saline-injected irradiated and sham-irradiated mice and 12 each for the 5-HT-treated mice). A significant increase was observed in the final colonic temperature of mice exposed at 1, 5, or 10 mW/cm^2 for 15 min. The hypothermic effect of 5-HT was evident whether the mice were exposed to microwaves or not. Both sham- and microwave-irradiated 5-HT-injected mice had lower colonic temperatures than 0 mW/cm^2 saline-injected mice. No significant increase was observed in the colonic temperature of saline-injected mice irradiated at 10 mW/cm^2. Analysis of the temperature change data ΔT (Table I) between microwave- and sham-irradiated 5-HT-treated BALB/C mice indicated statistically significant differences ($P < 0.01$, Student's t test) at each power density. Uninjected (i.e., no 5-HT or saline) BALB/C mice that were irradiated at a power density as high as 30 mW/cm^2, 2450 MHz for 30 min showed no increase in colonic temperature compared with sham-irradiated mice (9). The final temperatures for microwave (30 mW/cm^2) and sham-irradiated BALB/C mice were 38.1 ± 0.3 and 38.0 ± 0.3 ($\bar{X}$ ± SD, $N = 20$), respectively.

Figure 4 shows the effect of microwaves on the colonic temperature of CBA/J mice ($N = 12$ for each data point). A significant increase in the colonic temperature was observed at 5 and 10 mW/cm^2. At 1 and 0.5 mW/cm^2, while increases were observed in the final colonic temperature, these increases were not found to be

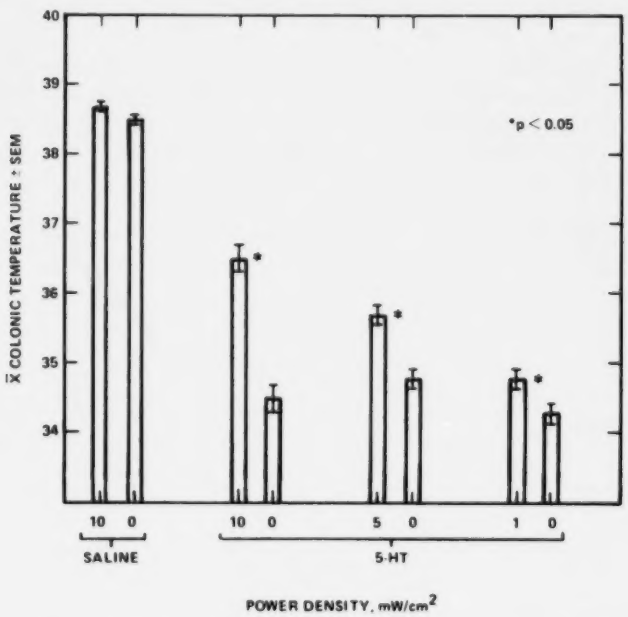

FIG. 3. Effect of 2450-MHz microwaves on the colonic temperature of 5-HT-induced hypothermic BALB/C mice. Mice were maintained at 22°C and 50% relative humidity during the 15-min exposure period. $N = 8$–12.

TABLE I

Change in Colonic Temperature of Mice Exposed to 2450-MHz Microwaves for 15 min at 22°C. For BALB/C mice $N = 8$–12 and for CBA/J mice $N = 12$

MOUSE STRAIN	POWER DENSITY (mW/cm^2)	MEAN ΔT · SEM (C^o) SHAM-IRRADIATED	IRRADIATED	P
BALB/C	10[a]	-0.26 · 0.11	-0.22 · 0.08	N.S.[b]
	1	-4.45 · 0.19	-3.53 · 0.17	< 0.01
	5	-4.01 · 0.18	-3.26 · 0.13	< 0.01
	10	-4.46 · 0.20	-2.43 · 0.26	< 0.001
CBA/J	10[a]	-0.67 · 0.19	-0.68 · 0.25	N.S.
	0.5	-4.35 · 0.26	-3.74 · 0.20	N.S.
	1	-4.18 · 0.11	-3.71 · 0.19	< 0.05
	5	-3.73 · 0.15	-2.93 · 0.19	< 0.01
	10	-3.90 · 0.17	-1.91 · 0.17	< 0.05

[a] SALINE INJECTED MICE
[b] NOT SIGNIFICANT, STUDENT'S T-TEST

statistically significant. Analysis of the ΔT data (Table I) between microwave- and sham-irradiated 5-HT-treated CBA/J mice, however, indicated a significant difference ($P < 0.05$, Student's t test) at incident power densities of 1, 5, and 10 mW/cm^2 but not at 0.5 mW/cm^2. No significant difference was observed in the colonic

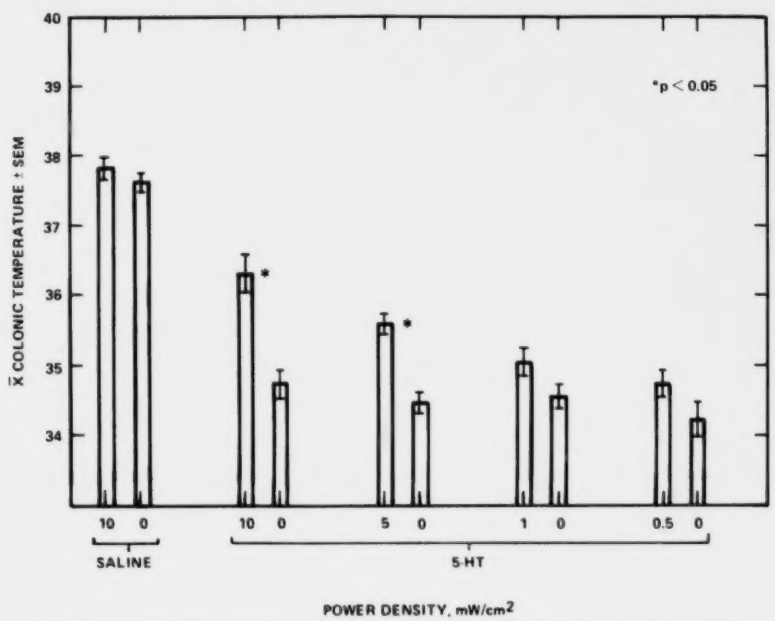

FIG. 4. Effect of 2450-MHz microwaves on the colonic temperature of 5-HT-induced hypothermic CBA/J mice. Mice were maintained at 22°C and 50% relative humidity during the 15-min exposure period, $N = 12$.

temperature or ΔT of saline-injected mice irradiated at 10 mW/cm^2 compared with saline-injected sham-irradiated mice.

To get an idea about the relationship between microwave heating and heating by convection in 5-HT-treated mice, an estimate of a microwave environmental equivalent was determined. Figures 5 and 6 show plots of the data (from Figs. 4 and 2, respectively) for CBA/J 5-HT-treated mice exposed to microwaves and mice held at different ambient temperatures. The slope of each line was determined by linear regression analysis. For the microwave data (Fig. 5), the slope is 0.1553. The slope of the line for the ambient temperature data is 0.2775. From these two values, a microwave dose/ambient temperature ratio of 1.79:1 is obtained. That is, under the conditions described, a power density of 1.79 mW/cm^2 2450-MHz microwave radiation will cause an increase in the colonic temperature (0.3°C) of a 5-HT-treated CBA/J mouse that is equal to the colonic temperature increase produced by a 1°C increase in ambient temperature. A colonic temperature increase of 0.3°C at a power density of 1.8 mW/cm^2 agrees well with the temperature increase that is predicted by the specific absorption rate data. At 1 mW/cm^2, a model comparable to a mouse absorbing energy at a rate of 0.7 mW/g over a 15-min period would display an increase in temperature of approximately 0.15°C.

DISCUSSION

The results of this study demonstrate that subtle microwave heating can be detected in mice made hypothermic by 5-hydroxytryptamine. When 5-HT injected

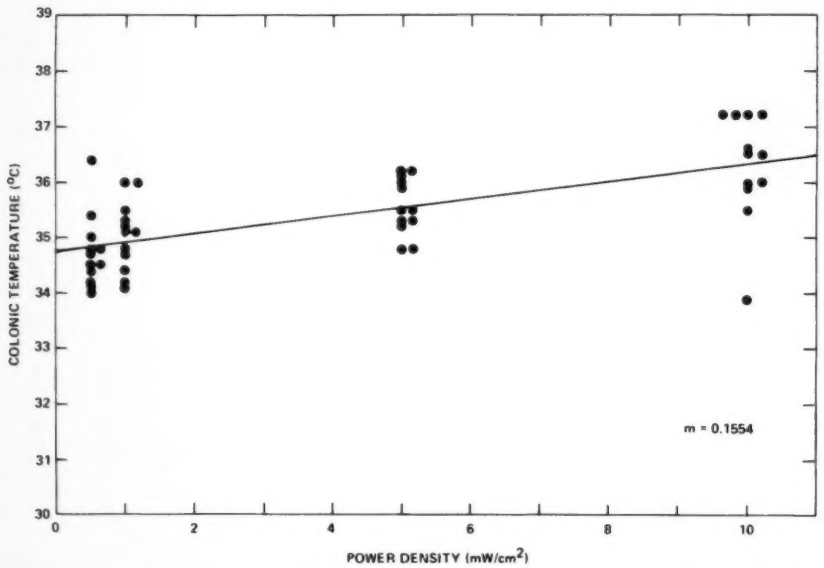

FIG. 5. Linear-regression plot of colonic temperature of 5-HT-treated CBA/J mice vs microwave power density. There was a significant ($P < 0.05$) positive linear dose-response relationship between microwave power density and colonic temperature of mice, with a correlation coefficient of 0.6557.

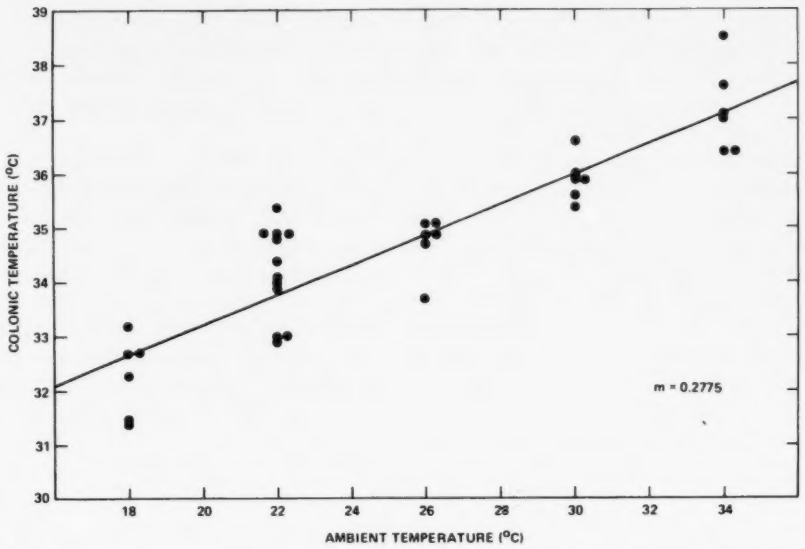

FIG. 6. Linear-regression plot of colonic temperature of 5-HT-treated CBA/J mice vs ambient temperature. There was a significant ($P < 0.05$) positive linear dose–response relationship between ambient temperature and colonic temperature of mice, with a correlation coefficient of 0.8985.

mice were maintained at an ambient temperature of 22°C and were exposed to 2450 MHz at an incident power density as low as 1 mW/cm^2, significantly higher colonic temperatures were recorded compared with colonic temperatures of sham-irradiated 5-HT-injected mice. This response to microwaves was dependent on the power density at which the mice were exposed. No significant increase in the body temperature of mice injected with saline and irradiated at 10 mW/cm^2 was observed compared with sham-irradiated saline-injected mice. In saline-injected and uninjected (*9*) mice, it appears that heating by microwaves can be compensated by thermoregulatory mechanisms and no significant increase in colonic temperature occurs following microwave exposure. However, in the 5-HT injected mice, normal thermoregulatory mechanisms were impaired by this drug and consequently microwave heating caused an increase in core temperature. Heat from the ambient environment also caused an increase in core temperature of 5-HT injected mice.

The mechanism(s) by which 5-HT alters the thermoregulatory system and makes mice hypothermic is not fully understood. The intraperitoneal administration of high doses (>20 mg/kg) of 5-hydroxytryptamine in mice produces a hypothermia within a matter of minutes. The response reported here is not unlike that reported by others (*7*, *10–12*). The intraventricular injection of a much lower dose of 5-HT (2 mg/kg) in mice produces a similar hypothermia (*13*). Francesconi and Mager (*14*) reported that the hypothermia produced in rats treated with L-tryptophan (a precursor of 5-HT) and held at 4°C resulted from a decrement in the stimulated heat production necessary to maintain a normal core temperature in a cold envi-

ronment and not to increased heat loss. While the hypothermia produced by intraventricular injection of 5-HT has been attributed to an interaction of 5-HT with receptors for this neurotransmitter in the brain (*13*), the parenteral administration of high doses (10–50 mg/kg) of 5-HT in mice appears to predominantly act peripherally rather than centrally (*12*).

Hypothermia can also be produced in mice (*15*) and rats (*5*) following the administration of bacterial endotoxin. This endotoxin-induced hypothermia, unlike the febrile response to endotoxin in larger mammals, is apparently due to the unfavorable ratio of surface area to body mass in the smaller-sized rodents (*16*). We have demonstrated that endotoxin-induced hypothermia in rats can be altered by 2450-MHz microwave radiation (*5*) in a manner similar to that reported here for 5-HT. This response to endotoxin in rats was dependent upon increases in the incident power density to which the rats were exposed. A correlation was also observed between ambient temperature and colonic temperature in endotoxin-treated rats as it was observed here for 5-HT-treated mice. Together these results indicate that microwave-induced heating is responsible for the increase in core temperature of endotoxin-treated rats and 5-HT-treated mice. These two models of chemically induced hypothermia may be useful for measuring microwave absorption in animals as suggested by Putthoff *et al.* (*6*) in their work with rats made hypothermic with cortisone or salicylate.

During drug-induced hypothermia, very subtle thermalization by low-intensity microwave radiation was detectable as a significant increase in body temperature. No body temperature change was observed in normothermic mice (i.e., mice injected with saline) exposed to microwaves at an incident power density 10 times that needed to produce a rise in core temperature of hypothermic mice. The response by increase in core temperature of 5-HT-treated mice to microwave radiation or increased ambient temperature indicates that microwave heating is responsible for the observed effect.

In light of these findings, as well as those reported elsewhere (*5*), more prudent assessment of claims in the literature for "nonthermal" (i.e., lack of measurable elevation of body temperature) microwave-induced biological effects in experimental animals is warranted. Furthermore, these results indicate that the interpretation of microwave-induced effects should include a consideration of the thermogenic potential of microwaves.

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